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Rosemarie Henson, M.S.S.W., M.P.H.
Director, Office on Smoking and Health
National Center for Chronic Disease Prevention
and Health Promotion
3005 Chamblee Tucker Road
Mail Stop K50
Atlanta, GA 30341-3724

Dear Ms. Henson:

Denise Keane shared with me your letters of June 3 and 20, 2003. I am responding to both requests in this single writing because they relate to one another in the broader context of investigating and reducing the harmful health effects of smoking. Instead of simply providing you with what potentially could be a large volume of raw scientific data, I will try to share with you a sense of the types of data we have on the areas of your request and on the broader context. My hope is that this will lead to further discussions where we can then address your requests for information with focused responses and relevant data. Of course we want to provide you with all responsive information we have that you would like so that we can address your questions properly and thereby have a meaningful dialogue.

Regarding your request on the levels of tobacco-specific nitrosamines (TSNAs) and other smoke constituents, we have the following types of data (some are brand specific, some are not):

- For the assessment of whether a new ingredient, material, process or design gives rise to increased toxicity or adds new toxic effects relative to an appropriate reference cigarette, we have generated data regarding levels of tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, aza-arenes, aromatic and heterocyclic amines, aldehydes, volatile organic compounds and inorganic compounds.

- One smoke chemistry study ('Massachusetts Benchmark Study') which may interest you was performed for the Massachusetts Department of Public Health (MDPH) in 1999. The study objective included measurement of the smoke chemistry of 28 selected commercial cigarette brands from products of the four leading domestic cigarette manufacturers at MDPH-defined machine smoking conditions. Mathematical relationships developed between smoke constituent yields and either tar, nicotine, or carbon monoxide might then be used to predict yields of other brands with design features within the range of the study cigarettes.

- In a study ('Global Benchmark Study') that began in 2001, we measured the smoke constituent yields from six brand styles of cigarettes manufactured by Philip Morris USA, and 42 brand styles of cigarettes manufactured by international affiliates of PM USA at several machine smoking conditions. The study objective was again to try to develop mathematical relationships between the yields of constituents at different machine smoking conditions, and to investigate the predictability of yields from other brand styles.

- In a 2002 study ('Market Mapping Study'), smoke constituents yields under Federal Trade Commission (FTC) conditions were measured for 26 US commercial cigarettes (including 11 PM USA brands) representing a range of FTC tar yields and manufacturers. This study provided information about current market brand smoke chemistry variation at FTC conditions, concentrating on cigarettes with the most common circumference, lengths, and filter designs. Average yields and ranges for each constituent as a function of FTC tar yield could then be used as a reference in new product development.

- In another 2002 study ('Brands Study'), eight conventional cigarettes from the US commercial market, representing a cross-section of design parameters and manufactured by PM USA, several standard reference cigarettes, and a prototype of an electrically heated cigarette smoking system from PM USA were smoked under FTC/ISO (International Organization for Standardization) and MDPH conditions. This study established correlations between smoke constituent yields within and between smoking conditions that may facilitate comparison and interpretation of smoke chemistry and other experimental data generated under various smoking conditions.

- Several studies related to TSNA levels in individual types of tobacco and tobacco products have been generated for our current TSNA-reduction program involving work with flue-cured tobacco growers to return to the use of indirect heating systems with heat exchangers during the tobacco curing process and our ongoing burley tobacco TSNA-reduction research efforts.

- If you have identified specific data sets of ours related to smoke constituents that you are particularly interested in, or there are other types of data you are looking for, please let me know.

Given that within the scientific community no consensus currently exists as to what specifically in smoke causes harm, we believe that this smoke chemistry information should be evaluated in the broader context of not only a sufficiently representative list of potentially harmful smoke constituents, but also of measured biological activity of that smoke. In addition, other relevant information, such as mechanistic, clinical and epidemiological data, has a bearing on the interpretation of the potential relevance of this information.

Important details must be addressed in order to properly evaluate such data, such as the characterization of the variability in the results and the selection of the appropriate reference or references. Tobacco, being a natural agricultural product, inherently has some variability in its chemical composition over time. We have performed limited monitoring of smoke constituent yields over time, where this variability is seen in cigarette smoke composition. Another source of variability of smoke constituent yields can be the lack of standardized methods between laboratories. Some data we have relevant to the consideration of variability include:

- Levels in an internal control cigarette which is made new, but to a fixed specification, for each study, over many years (this provides information on the variability caused by the natural variation in tobacco from year to year as well as the manufacturing variability, based on results obtained in at least one laboratory)

- Levels in the standard reference cigarette 1R4F, made in one batch in 1983, have been determined repeatedly over many years (this provides insight into the assay variability at least within two laboratories)

- Data from our most recent on-going inter-laboratory study, using five commercial and three standard reference cigarettes (this provides information on the variability of smoke chemistry analysis data under various machine smoking conditions between different laboratories, ours and several commercial laboratories)

Regarding your request for smoking behavior information, another important part of addressing the harm of smoking, we have the following types of recent information:

- We have conducted two types of human switching studies during which many of the topography measures you ask about (puff volume, puff duration and inter-puff intervals) have been measured. These studies are of two basic designs: controlled, during which the subjects live in a clinical environment for the duration of the study, and ambulatory, during which subjects continue their typical daily activities at home and at work, and visit the clinic for sampling of biofluids and topography measurements. Some of these studies have data available now, and others will in the future. An important point is that the levels of smoke constituents or their metabolites in biofluids, which are a more direct measure of actual smoke exposure, are the primary measurements made in these studies, and that data can be reviewed along with any topography measurements. In addition, we have assessed, through subject questionnaires, patterns of smoking and consumption and the subjects' rating of cigarette attributes.

- In addition to the clinical switching studies, we are also in the process of determining a US population baseline for cigarette smoke exposure by conducting a multi-center study to determine the exposure of adult smokers to cigarette smoke. This baseline will be derived from the measurement of biomarkers of exposure in adult smokers who regularly smoke brands representative of tar and nicotine yields in the US, as measured by the FTC method. We have completed a pilot study involving 69 adult smokers and 67 adult non-smokers. The full study, which is designed to evaluate exposure in 4000 adult smokers and 1000 adult non-smokers (as a control group) at 41 study sites across the US, is currently underway.

- Again, if you have identified specific data sets of ours related to smoking behavior that you are particularly interested in, or there are other types of data you are looking for, please let me know.

An important point to emphasize is that puffing parameters (as measured by smoking topography) are only a part of the smoking behavior that determines smoke exposure. Since smoking

topography cannot measure depth of inhalation, for example, biomarkers of exposure are an important tool for properly quantifying internal dose.

Further, the types of information you specifically requested comprise several, but not all, of the elements necessary in addressing the harm caused by cigarettes. Accordingly, I think it is important to consider this information in the full context of the types of data, methods and assessment processes that would add rigor to any interpretation. Such a context was identified by the Institute of Medicine (IOM) in its 2001 report 'Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction' (the 'IOM Report'), in which important public health concerns, such as adverse impact on initiation and cessation, are addressed. We have used that model to develop a process for assessing the potential for harm reduction of new cigarette technologies and products. This process includes a weight of evidence approach that takes into account data from a battery of chemical and toxicological tests, as well as data from clinical studies. A graph summarizing that process is attached, and some items worth highlighting follow:

- Non-clinical evaluations

  To assess whether a new ingredient, material, process or design gives rise to increased toxicity or adds new toxic effects relative to an appropriate reference cigarette, we run a battery of sensitive, comparative chemical and biological analyses on the cigarette smoke, including smoke chemistry and the evaluation of effects in cellular and laboratory animal models relevant to the diseases caused by smoking. These studies are usually done under FTC or ISO smoking conditions. We also have one study completed under conditions that more closely reflect how adult smokers smoke the tested products. Data from such studies contribute to the assessment of potential increased toxicity and, as the case may be, reductions in toxicity or smoke exposure.

  While these data are important as a component for the weight of evidence assessment, they do not substitute for direct human exposure assessment.

- Clinical exposure

  Although smoking topography measures of the type described in your request are taken in clinical exposure evaluations, exposure in adult smokers is better determined by the levels of smoke constituents or their metabolites in appropriate biofluids. Biomarkers of effect, complementing disease endpoints determined in non-clinical studies, are currently being developed. When evaluating products, these studies are conducted with smokers switching from their current brand, and are of two basic designs described above: controlled, during which the subjects live in a clinical environment for the duration of the study, and ambulatory, during which subjects continue their typical daily activities at home and at work, and visit the clinic for sampling of biofluids. In addition, as mentioned above, a large population study (not a switching study) we are conducting with almost 5,000 subjects will help characterize the current market place and thereby provide a point of reference for interpreting these data.

- Surveillance

In all of this, an important part is surveillance. When done for a potential reduced exposure product, post-market surveillance would, among other things, provide monitoring of the population effects, taking into account impact on initiation and cessation rates, watching the long-term exposure and health of individual adult smokers using such products, as well as the impact on the smoker population. We have developed a post-market surveillance plan for the ongoing and systematic collection, analysis, interpretation and dissemination of data regarding the use of the potential reduced exposure/risk products that PM USA intends to introduce into the marketplace.

Surveillance is an area in which we would particularly appreciate an opportunity to discuss with you and receive input on the approach we are currently planning.

In providing you with information, one thing you should note is that references to many of our publications and presentations are also listed on a bibliographic website that PM USA created for scientists and public health professionals (www.ehcss-science.com). The 'Methods Bibliography' section of the website contains references which are pertinent to elements of the harm reduction assessment process highlighted above. Another source of relevant documents is the PM USA document site (www.pmdocs.com).

Harm reduction and its assessment, including the specific issues you have raised, challenge numerous scientific disciplines. This requires both a good understanding of the overall scientific principles and processes as well as the scientific and technical details. Therefore, we believe that scientific/technical meetings between your and our scientific experts would be an effective means for sharing learnings and information responsive to your requests within a relatively short period of time. Such an interactive format would optimize the opportunity for clarification of your interests and our ability to provide the information you would like to receive. Also, as we collected new information on exposure and risk reduction and its assessment, we have identified research areas that need to be addressed in order to be successful and diligent in such a pursuit. This is an evolving capability, as the IOM Report indicated it would be. We would like to share with you our thinking, knowledge and data on all these topics, while also addressing your specific requests.

As indicated previously by our Chairman and CEO, Mike Szymanczyk, in his letter to Dr. Marks on June 5, 2003, PM USA looks forward to contributing our knowledge and data to achieving a better understanding of and reduction in the harm of smoking and in defining the best possible way forward to fill the numerous gaps in our understanding while addressing issues important to you as a governmental public health organization.

I am copying this letter to Dr. P. Richter who was identified by you as a point of contact in your organization and with whom I had a telephone conversation recently regarding this response. Given the breadth of the potential subject matter, and my strong belief in the importance of having the input of a broad variety of experts, I would also like to share this letter with some scientists and public health experts who have expert knowledge and interest in this area, and those who have contributed to defining the objective scientific process; for example, members of the committee who authored the IOM Report and many scientists who participated in the deliberations of the committee. To this end, please let me know if you have any objection.

We are committed to reducing the harm from cigarette smoking. Smokers should quit smoking or not start smoking in the first place as the best option to reduce the health effects of smoking. For those who nonetheless choose to smoke, we are committed to developing new cigarette technologies and products that have the potential to reduce the harm from smoking.

We will make our scientific experts available to discuss any or all of the elements outlined above at your earliest convenience. Please don't hesitate to call me to discuss at (804) 274-4011.

Sincerely,

Attachment – 1

cc: Denise F. Keane, Philip Morris USA
Dr. James S. Marks, CDC
Dr. Patricia Richter, CDC